for one of the mistletoe lectin polypeptide isoforms identified in mistletoe cells and/or to optimize expression.

89. The process for production of a polypeptide of claim 46, including as a further step the modification of sugar side-chains by enzymatic and/or chemical addition, removal and/or modification of one or several side-chains.

90. The process of claim 89, wherein the addition, removal and/or modification or the sugar side-chain leads to matching to the natural proteins.

II. REMARKS

AMENDMENTS TO THE SPECIFICATION

By the foregoing amendment, the applicants have complied with the Sequence Listing rules by replacing the Sequence Listing of record with a substitute Sequence Listing, introducing SEQ ID numbers corresponding to the sequences disclosed throughout the specification, claims and figures (see enclosed computer readable copy, hard copy of the Sequence Listing, and Sequence Listing statement) and replaced pending claims with new claims 46-90.

The changes embodied in the substitute Sequence Listing pertain only to compliance with formatting rules. The substitute Sequence Listing corrects the "General Information" section of the Sequence Listing. In particular, the applicant name described under numeric identifier <110> has been corrected to reflect the applicant names (Morris, Peter; Stiefel, Thomas; Voelter, Wolfgang; and Welters, Peter). The file reference under numeric identifier <130> has been corrected to reflect a new reference number ("29841/36636"). The current application number ("09/601,667") and filing date ("2000-10-06") have been added as described in fields <140> and <141>, respectively. Also, prior application number ("PCT/EP99/00696") and prior application filing date ("1999-02-03") have been added as identified in fields <150> and <151>, respectively.

The <223> field of SEQ ID NO: 1 for amino acid position 500 has been amended to recite "product= "Xaa is Asn or Ser or Thr or Lys"/label=Xaa36". Support for this amendment is found throughout the application, particularly at page 7, line 3 and page 22, line 18. In addition, the "Artificial" sequence organisms throughout the sequence listing have been further described in the <220> to <223> feature section in order to comply with 37 C.R.R. §1.823 (b). Also, the sequence of SEQ ID NOS: 37, 38 and 39 have been added and find support in the figures as originally filed. Particularly, SEQ ID NOS: 37-39 are disclosed in figures 2b, 3b and 5b, respectively of the application as originally filed.

AMENDMENT TO THE CLAIMS

By the foregoing amendment to the claims, the applicants have simply rewritten the claims to correct minor informalities, replace references to sequences with sequence identification numbers, remove the multiple dependancies from the claims and have renumbered the claims as a convenience to the examiner. Therefore, no new matter has been added.

III. CONCLUSION

In view of the foregoing, the applicants respectfully request that substantive examination be undertaken.

Respectfully submitted,

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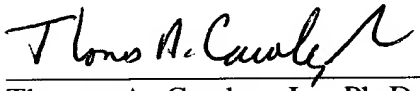
By: 

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March 11, 2002

MARKINGS SHOWING CHANGES MADE TO SPECIFICATION

At page 5, beginning at line 20 has been amended as follows:

Hence the present invention makes available a process for the production of a mistletoe lectin polypeptide or a fragment thereof in the heterologous system having the following sequence (SEQ ID NO: 1):

At page 7, beginning at line 5-7 has been amended as follows:

Analogously to this process, two further production processes for the mistletoe lectin A-chain (MLA) (SEQ ID NO:2) and mistletoe lectin B-chain (MLB) (SEQ ID NO: 3) are made available, which contain the following sequences or a fragment thereof:

At page 8, beginning at line 15 has been amended as follows:

Furthermore, a mistletoe lectin polypeptide or a fragment thereof, which includes the sequence variability of the various MLA and MLB chains, having the following sequence is provided (SEQ ID NO: 1):

At page 10, beginning at line 3 has been amended as follows:

Apart from this, mistletoe lectin polypeptides of the mistletoe lectin A-chain (SEQ I D NO: 2) and mistletoe lectin B-chain (SEQ ID NO: 3) or fragments of these sequences are provided, which include the following sequences:

The paragraph at page 11, beginning at line 17 has been amended as follows:

The sequence which includes the above-described variability of the ML-I polypeptides occurring in mistletoe cells is shown in Figure 1b (SEQ ID NO: 4). A specific sequence for MLA2 of mistletoe lectin I, which was likewise produced according to the process

presented above, is shown in Figure 3b (SEQ ID NO: 38). Figures 7b to 12b (SEQ ID NOS: 6-11) include specific mistletoe lectin B-chain sequences, which were likewise produced according to the process described above.

At page 12, beginning at line 5 has been amended as follows:

b) amplifying mistletoe cell RNA or chromosomal mistletoe lectin DNA by PCR using oligonucleotides which are derived from the mistletoe lectin polypeptide shown in Fig. 1b (SEQ ID NO: 4), and

At page 12, line 23 has been amended as follows:

GTN MGN GAY GAY GAY TTY CA (SEQ ID NO:33):

At page 12, line 25 has been amended as follows:

AT YTG RTT NGG YTT NCC NGT (SEQ ID NO: 34):

The paragraph at page 13, beginning at line 3 has been amended as follows:

In a further reaction step, using specific oligonucleotides, the 5'- and 3'-lying sequences of the first amplification product were determined by means of the RACE technique (Example 3). The oligonucleotide used for the 5'-RACE reaction has the following sequence (SEQ ID NO: 35):

At page 13, beginning at line 7 has been amended as follows:

The oligonucleotide used for the 3'-RACE reaction has the following sequence (SEQ ID NO: 36):

At page 13, beginning at line 20 has been amended as follows:

Nucleic acid molecules which are made available by this process and code for a polypeptide as described above, include the following sequences for ML-I (SEQ ID NO: 12), MLA (SEQ ID NO: 13) and MLB (SEQ ID NO: 14) or fragments thereof:

The paragraph at page 16, beginning at line 18 has been amended as follows:

A specific nucleic acid molecule which was prepared by the process stated above and includes the entire ML-I coding sequence, is shown in Figure 1a (SEQ ID NO: 15). Further specific nucleic acid molecules, which code for the MLA chain of mistletoe lectin I and were prepared by the process stated above, are shown in Figure 2a (SEQ ID NO: 16) and Figure 2b (SEQ ID NO: 37). Specific sequences for MLB nucleic acid molecules, which were prepared by the process described above, are listed in Figures 7a to 12a (SEQ ID NOS: 21-26). Here, each of theses nucleic acid sequences codes for a polypeptide which emerged by protein sequencing of the ML-I mixture from natural mistletoe extract.

The paragraph at page 17, beginning at line 3 has been amended as follows;

In addition, the present invention includes nucleic acid molecules which code for a mistletoe lectin polypeptide, as described above, and are [characterised] characterized in that the codon usage is matched to the requirements of a heterologous host. Figure 4a (SEQ ID NO: 18) shows such a nucleic acid sequence, wherein the codon usage is matched to the preferred codon usage of the genus *Brassica*. This genus was chosen, since both as the Summer and also as the Winter form it thrives outstandingly in the middle latitudes of Europe, North America and Asia. The possible uses of rape for the production of recombinant proteins have been demonstrated by various firms and research institutes. Examples, of its use are the production of gastric lipase for use in the treatment of cystic fibrosis or coupling to oleosins for greater ease of purification of the recombinant proteins from the lipid phase of the rape oil seeds.

The paragraph at page 17, beginning at line 13 has been amended as follows:

The sequences shown in Figures 5a (SEQ ID NO: 19), 6a (SEQ ID NO: 20), and 13a to 18a (SEQ ID NOS: 27-32) represent nucleic acid molecules which code for MLA polypeptides or for MLB polypeptides of mistletoe lectin I and whose codon usage is likewise matched to the genus *Brassica*. The degree of homology between these matched sequences to the nucleic acid sequences shown in Figs 2a (SEQ ID NO: 16) and 7a (SEQ ID NO:21) is ca. 61% for MLA and about 63% for MLB.

At page 20, beginning at line 27 has been amended as follows:

Furthermore, the present invention also includes a process for the production of a mistletoe lectin polypeptide in mistletoe cells and/or transgenic mistletoe plants having the following sequence (SEQ ID NO: 1).

At page 22, beginning at line 20 has been amended as follows:

On the basis of the process described above, two further production processes for the ~~mistletoe lectin A-chain (SEQ ID NO: 2) and mistletoe lectin B-chain (SEQ ID NO: 3)~~ or a fragment thereof are provided, which contain the following sequences or a fragment thereof:

The paragraph at page 24, beginning at line 20 has been amended as follows:

Firstly, plant RNA or DNA is isolated preferably from fresh material by various generally known processes (Quiagen experimental protocol, Nickrent D L et al., American Journal of Botany, vol. 81, No. 9 (1994): 1149-1160; Example 1). Using the degenerate oligonucleotides BI and BII described in Example 1, which are derived from the mistletoe lectin polypeptide shown in Figure 1b (SEQ ID NO: 4), the mistletoe lectin-I gene is amplified in a PCR reaction, the conditions for which are set out in Example 2. If this amplification step does not include the complete open reading frame of ML-I, the 5' and 3' region of the amplified nucleic acids can be identified using the RACE technique with the respective oligonucleotides stated in Example 3. The nucleic acid molecules thus

obtained are isolated and if necessary ligated into a vector using suitable restriction cleavage sites in such a way that this contains the complete open reading frame. A nucleic acid molecule or a fragment thereof contained in this vector, which codes for a polypeptide such as described above in a mistletoe cell or a transgenic mistletoe plant, comprises the following sequence (SEQ ID NO: 12):

At page 26, beginning at line 15 has been amended as follows:

A nucleic acid molecule according to the invention or a fragment thereof, which codes for one of the above-mentioned MLA polypeptides in a mistletoe cell or a transgenic mistletoe plant, comprises the following sequence (SEQ ID NO: 13):

The paragraph at page 27, beginning at line 13 has been amended as follows:

Furthermore, a nucleic acid molecule or a fragment thereof, which codes for one of the above-mentioned MLB polypeptides in a mistletoe cell or a transgenic mistletoe plant, ~~having the following sequence is made available~~ (SEQ ID NO: 14):

The paragraph at page 28, beginning at line 18 has been amended as follows:

A specific nucleic acid molecule which is to be expressed in a mistletoe cell or in a transgenic mistletoe plant and codes for ML-I, is shown in Figure 1a (SEQ ID NO: 15). Further specific nucleic acid plants, which are modified in their codon usage in such a manner that as a result the expression rate is [optimised] optimized.

The paragraph at page 29, beginning at line 14 has been amended as follows:

The following figures and examples illustrate the invention:
Fig. A: Representation of a mistletoe lectin-I dimer.
Fig. 1: Representation of the (a) nucleic acid sequence (SEQ ID NO: 15) and (b) amino acid sequence (SEQ ID NO: 4) of MLA-I.

Fig. 2: Representation of the (a) nucleic acid sequence (SEQ ID NO: 16) and (b) amino acid sequence (SEQ ID NO: 37) of mistletoe lectin A1.

Fig. 3: Representation of the (a) nucleic acid sequence (SEQ ID NO: 17) and (b) amino acid sequence (SEQ ID NO: 38) of mistletoe lectin A2.

Fig. 4: Representation of (a) the nucleic acid sequence of MLI (SEQ ID NO: 18), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin I (matched) (SEQ ID NO: 4).

Fig. 5: Representation of the nucleic acid sequence of mistletoe lectin A1 (SEQ ID NO: 19), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin A1 (matched) (SEQ ID NO: 39).

Fig. 6: Representation of (a) the nucleic acid sequence of mistletoe lectin A2 (SEQ ID NO: 20), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin A2 (matched) (SEQ ID NO: 5).

Fig. 7: Representation of the (a) nucleic acid sequence (SEQ ID NO: 21) and (b) amino acid sequence (SEQ ID NO: 6) of mistletoe lectin B.

Fig. 8: Representation of the (a) nucleic acid sequence (SEQ ID NO: 22) and (b) amino acid sequence (SEQ ID NO: 7) of mistletoe lectin B1.

Fig. 9: Representation of the (a) nucleic acid sequence (SEQ ID NO:23) and (b) amino acid sequence (SEQ ID NO: 8) of mistletoe lectin B2.

Fig. 10: Representation of the (a) nucleic acid sequence (SEQ ID NO:24) and (b) amino acid sequence (SEQ ID NO: 9) of mistletoe lectin B3.

Fig. 11: Representation of the (a) nucleic acid sequence (SEQ ID NO:25) and (b) amino acid sequence (SEQ ID NO: 10) of mistletoe lectin B4.

Fig. 12: Representation of the (a) nucleic acid sequence (SEQ ID NO:26) and (b) amino acid sequence (SEQ ID NO: 11) of mistletoe lectin B5.

Fig. 13: Representation of (a) the nucleic acid sequence of mistletoe lectin B (SEQ ID NO:27), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B (matched) (SEQ ID NO: 6).

Fig. 14: Representation of (a) the nucleic acid sequence of mistletoe lectin B1 (SEQ ID NO:28), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin 1 (matched) (SEQ ID NO: 7).

Fig. 15: Representation of (a) the nucleic acid sequence of mistletoe lectin B2 (SEQ ID NO:29), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B2 (matched) (SEQ ID NO: 8).

Fig. 16: Representation of (a) the nucleic acid sequence of mistletoe lectin B3 (SEQ ID NO:30), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B3 (matched) (SEQ ID NO: 9).

Fig. 17: Representation of (a) the nucleic acid sequence of mistletoe lectin B4 (SEQ ID NO:31), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B4 (matched) (SEQ ID NO: 10).

Fig. 18: Representation of the (a) nucleic acid sequence of mistletoe lectin B5 (SEQ ID NO:32), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B5 (SEQ ID NO: 11).

At page 31, line 12 has been amended as follows:

B1. GTN MGN GAY GAY GAY TTY CA (SEQ ID NO: 33)

At page 31, line 13 has been amended as follows:

B2. AT YTG RTT NGG YTT NCC NGT (SEQ ID NO: 34)

At page 32, line 3 has been amended as follows:

CAC AGC AGT ATT ACA GTC GAA (SEQ ID NO: 35).

At page 32, line 4 has been amended as follows:

GTC TAT GTG ATG ATC TTC GAC TGT (SEQ ID NO: 36).